NASA TECHNICAL TRANSLATION NASA TT F-15,874

BETA-FETOPROTEIN IN SYSTEMIC LUPUS ERYTHEMATOSUS

S.S. Vasileyskiy, V.A. Nasonova, R.V. Petrov, and O.M. Folomeyeva

Translation of "β-fetoprotein pri sistemnoy krasnoy volchanke," Terapevticheskiy Arkhiv, Vol. 46, No. 3, 1974, pp. 137-143

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
WASHINGTON, D.C. 20546 AUGUST 1974

STANDARD TITLE PAGE

1. Report No. NASA TT F-15,874	2. Government Accession No.	3. Recipient's Catalog No.
4. Title and Subtitle BETA-FETOPROTEIN IN SYSTEMIC LUPUS ERYTHEMATOSUS		5. Report Date August 1974 6. Performing Organization Code
7. Author(s) S.S. Vasileyskiy, V.A. Nasonova, R.V. Petrov, O.M. Folomeyeva, II Moscow Medical Institute and USSR Academy of Medical Sciences Institute of Rheumatism		8. Performing Organization Report No. 10. Work Unit No.
9. Performing Organization Name and Address Leo Kanner Associates Redwood City, California 94063		11. Contract or Grant No. NASw-2481 13. Type of Report and Period Covered Translation
12. Sponsoring Agency Name and Address National Aeronautics and Space Administration, Washington, D.C. 20546		14. Sponsoring Agency Code

15. Supplementary Notes

Translation of "β-fetoprotein pri sistemnoy krasnoy volchanke," Terapevticheskiy Arkhiv, Vol. 46, No. 3, 1974, pp. 137-143

16. Abstract Data are presented on clinical-laboratory study of 14 systemic lupus erythematosus patients including descriptions of antiserum production, immunoelectrophoresis procedures and the age and length of disease distribution of the patients. Detailed case histories are presented for three patients, in whom β_2-fetoprotein was found. It is concluded that further research is necessary for accumulation of data on the diagnostic and prognostic value of the appearance of β_2-fetoprotein and use of systemic lupus erythematosus as a model of an autoimmune disease system in solution of problems in immunogenesis. A more direct comparison of β_2-fetoprotein with the IgM$_S$ monomer should be made.

17. Key Words (Selected by Author(s))	18. Distribution Statement Unclassified-Unlimited		
19. Security Classif. (of this report) Unclassified	20. Security Classif. (of this page) Unclassified	21. No. of Pages 17	22. Price

BETA-FETOPROTEIN IN SYSTEMIC LUPUS ERYTHEMATOSUS

S.S. Vasileyskiy, V.A. Nasonova, R.V. Petrov, and
O.M. Folomeyeva,
II Moscow Medical Institute and USSR Academy of Medical Sciences
Institute of Rheumatism

We have previously (S.S. Vasileyskiy and V. I. Yablokova, 1964-1967) described two fetal proteins, β_1 and β_2 of the blood serum globulin fractions of a newborn child. One of these proteins, β_1-fetoprotein, has been studied independently of us by Yu. S. Tatarinov. Subsequently, both proteins were systematically studied by the French immunochemists Uriel and colleagues and de Nechand and colleagues. /137*

The embryonic protein β_2-fetoprotein was discovered in a congenital immunodeficit with ataxia telangiectasia (S.S. Vasileyskiy, Yu. M. Lopukhin, R. V. Petrov).

Since it is known that dysfunction of the immune system is noted in systemic lupus erythematosis (SLE), it was decided to examine SLE patients for the presence of one of the fetal proteins, β-fetoprotein, in the blood serum. The appearance of a fragment of the pentameric immunoglobulin M molecule, the IgMs monomer, was observed in precisely these two clinically unrelated disease manifestations (Rothfield, Frangione and Franklin, Stobo and Tomasi), in which IgMs, like β_2-fetoprotein, is not encountered in the blood of a healthy man in the free, monomeric state and is, in the strict sense of the word, a fetal protein. There are no fetal protein analogs in a healthy adult body, as with fetal hemoglobin, both embryonic hemoglobins (Gower -- 1 and 2), fetuin and α-fetoprotein. Synthesis of these proteins normally stops in

---

* Numbers in the margin indicate pagination in the foreign text.

the neonatal period, but it is renewed in some pathological states in adults.

Antiserum Production

Blood serum samples were taken from the umbilical cords of healthy, full-term neonates. Rabbits were immunized with the β-fraction of this serum, obtained by agar block electrophoresis. The β-fraction preparation obtained from 5 ml of neonate serum was used for each injection. The immunization scheme: three injections at 10 day intervals; after a break of 1-2 months, the first reimmunization; then, after a 2 month break, the second reimmunization and, finally, blood collection on the seventh day after the second reimmunization.

Immunodiffusion Technique

Electrophoresis was carried out in 1% agar gel in 0.05 M veronal buffer, pH 8.6; layer thickness 2 mm; voltage gradient 5V/cm; electrophoresis time 1 hour. Immunodevelopment was carried out in the classical version, with a longitudinal groove, as well as in the modification which we described earlier (S. S. Vasil-eyskiy, V.I. Yablokova, 1964): after switching off the current, the antiserum was poured into a groove, which was cut perpendicular to the electrophoresis axis, 5 mm towards the cathode from the edge of the β fraction. The sample sequence is the following: the neonatal serum was located beside the serum of a healthy person and further on, a cell with the test sample. The preparations were stained with amido black. In individual cases, two stains were combined in the same preparation, by alternating rectangular amido black and benzidine bands. Staining, in which the dividing line passes through the center of the arc, is especially significant. A water color brush was used for convenience in application of the reagents in these bands. The

reagents were used, in the form of a saturated solution of benzidine in a 20% acetic acid solution, with 0.3 ml H_2O added per 10 ml of solution.

Chromatography was carried out on Sephadex G-200, in the following manner. The neonatal serum mixture was dialyzed against the buffer in which the entire chromatographic procedure was then carried out, and it was applied in the amount of 0.5 ml to a column with fine-grained Sephadex G-200. The column dimensions were 20 x 300 mm. There was a 140 mm column of buffer above the upper level of the gel grain suspension. Both for suspension of the Sephadex and for elution (i.e. as the chromatographic development), 0.05 M veronal buffer pH 8.5, with addition of NaCl to 0.5 M, was used. The duration of the chromatographic process was 3 1/2 hours. Eighteen samples (of 6 ml each) were collected in this time. The IgM and IgG concentrations were measured in the same fractions, as mobility standards. The determination was carried out on Partigen plates (Hoechst, Behringwerke). The IgM peak arrived in the sixth fraction and the IgG, in the 10-12th fraction. /138

Twenty female patients were examined, of whom 14 suffered from SLE and, of the remainder, used as the control group, three with systemic scleroderma (SCL), one with dermatomyositis, one with primary amyloidosis and one with infectious-allergic syndrome (see table). The diagnosis was completely reliable in all SLE, SCL and dermatomyositis patients; primary amyloidosis was established upon autopsy (SLE was suspected in the patient in the clinic).

It is evident from the table that patients between 20 and 40 years old, with the disease lasting 5 years and more, predominated among the patients. Only three of the patients had not received prednisolone before admission to the Institute (two of them suffer from SCL and one from infectious-allergic syndrome), and the

GENERAL CHARACTERISTICS OF THOSE EXAMINED

Diagnosis	No. of patients	Age (in years)			Duration of disease (in years			
		Up to 20	Up to 40	Older than 40	Up to 1	Up to 5	Up to 10	Over 10
SLE	14	2	12	1	1	7	3	3
Other diseases (control)	6	--	4	2	--	4	2	

remaining ones had been treated with prednisolone for a period of many years and they usually had been on sustaining doses of it (from 5 to 15 mg per day) up to the time of examination.

The similarities of the basic and control groups were manifested in the nature of the course of the pathological process. Thus, SLE was subacute in four patients and chronic in four, SCLwas subacute in one patients and chronic in two (2). Thus, predominantly subacute and chronic courses were observed in patients with collagenoses (13 of 17). Since the patients, especially those with SLE, systematically took sustaining doses of prednisolone, there was I and II degree activity in ten of them, although the highly-active phase of SLE was typical in all of them in the past. III degree activity of the disease, in the form of polyarthritis, combined with active polyserositis (in two) and skin involvement ("butterfly") was noted in only four SLE patients. Of 14 examined, seven had lupus nephritis (active in five and inactive in two). In the remaining SCL, dermatomyositis and other patients, polyarthritis, polymyositis, Raynaud's phenomenon, myocardosis, etc., also were established. Consequently, an active clinical picture was typical of all patients in the past or at present.

β_2-fetoprotein was found in three patients. We present the observations.

Patient U, Age 27

In 1957, at age 11, acute arthritis of one of the knee joints developed after diphtheria. In the summer of 1961, after overcooling, arthralgia and in September of the same year, polyarthritis, subfebrility and a systolic murmur at the apex. He was treated with prednisolone, in connection with probable rheumocarditis, to good effect, but, after stopping the preparation, aggravation of the polyarthritis occurred in the talocalcanean, knee, radiocarpal and other joints, requiring renewal of prednisolone use. Rheumatoid arthritis was then diagnosed. The rheumatism was observed at the Institute, beginning in September 1962. From 1962 to 1967, a wave-like course of the polyarthritis was noted, with rises in temperature to 39°, sweating and acceleration of the ERS to 35-42 mm/hour during the period of aggravation. Prednisolone usually helped. The patient began to take prednisolone constantly (from 1/2 to 4 tablets) and aminoquinoline preparations in 1967.

Beginning in 1967, Raynaud's phenomena and unstable erythematose rashes on the face, in the "butterfly" zone, on the right shin, a diffuse II degree struma, vasomotor rhinitis, anemia /139
(hemoglobin down to 10.3 g%), continual acceleration of the ESR (up to 35 mm/hour) and hyperproteinemia (total protein 9 g%) were added to the recurring polyarthritis, with transient contractures and high temperatures.

After examination at the Institute of Rheumatism at the beginning of 1968, a diagnosis of SCL was made, in connection with persistent Raynaud's phenomenon and solid edema of the hands, transient rheumatoid arthritis (absence of bone destruction, despite the 7-year, almost continuous course of the disease).

Moreover, recurring polyserositis (pleurisy, pleural-pericardial adhesions and buildups), basal pneumofibrosis and focal myocarditis (perturbation of the rhythm, in the form of bigeminy and frequent extrasystoles) were then noted. A little anemia (hemoglobin 11 g%) and a ++ latex test at a 1/40 titer were found in laboratory examinations; LE cells and antibodies to DNA were not found.

Chronic synovitis, with productive vasculites, was established by biopsy of the synovial membrane.

In recent years, on a background of a persistent joint syndrome, without tendency toward deformation (only a slight ulnar deviation), a decrease in vasomotor disorders, disappearance of the solid edema and the same chronic synovitis upon repeated biopsy are noted; however, symptoms of nuclear pathology, infrequent small infiltrates of lympoid cells and, by laboratory examination, the former tendency towards hyperproteinemia (8.7-9.2 g%) appeared, antibodies to DNA (+++ in a 1/10 titer) and to nucleoproteids (++1/20) and cryoprecipitins up to ++++ were first found, and the complement level decreased (CH_{50} -- 30 units). The rheumatoid factor in the Rose-Waaler reaction had a titer of 1/32 (once) and in the latex test, ++ at a 1/40 titer. LE cells and the "rosette" phenomenon were first found.

The urea syndrome was added in 1971, with proteinurea up to 0.075 °/oo and changed erythrocytes and single hyaline cylinders in the field of view; protein 0.037 °/oo by the Kakovskiy-Addis test, Leukocytes 2,240,000, erythrocytes 160,000.

In the last examination in June-July 1972, considerable weight reduction was noted (47.5 kg at a height of 160 cm), and enlargement of in all groups of lymph nodes, disfiguration of the small and large joints of the extremities, transient flexing contracture in the elbow joints and friction noise of the pleura at the rear on both sides.

In X-ray photography of the hand and foot joints, epiphyseal osteoporosis, constriction of the gaps in the joints and single instances of wasting away of the bone and tissue at the edges were revealed. X-ray of the thoracic cage: thickening of the pleura, sinuses do not open, diaphragm located high at the right outline of the heart, pronounced pleuro-pericardial adhesions. The amplitude of kymogram spikes is decreased.

Blood analysis: hemoglobin 12 g%, leukocytes 5400, ESR 56 mm/hour. Total protein 8.7 g%, γ-globulins 31.9%, latex test and Rose-Waaler reactions negative, LE cells not detected. Antibodies to DNA at 1/10 titer +, nucleoproteids at 1/10 titer ++, cryoprecipitins +, CH_{50} 29 units. β_2-fetoprotein was detected, in the form of very intense arcs on the immunoelectrophoretogram (Fig. 2).

In the urine, proteins 0.3 °/oo, 3-4 leukocytes in field of view; Kakovskiy-Addis analysis, proteins 0.3 °/oo, erythrocytes 2,000,000, leukocytes 4,000,000, cylinders 200,000.

Thus, a persistent seronegative polyarthritis (chronic synovitis with solitary lymphoid infiltrates and nuclear pathology), but with little destructive change, is observed in the 27 year-old patient, which can be evaluated as chronic erythematous arthritis, with transient Raynaud's phenomenon and myocarditis, recurring polyserositis, pneumonitis and nonprogressing urea syndrome. The diagnosis of SLE is confirmed by the past presence of skin rashes in the "butterfly" zone, high titers of antibodies to DNA and nucleoproteids and the periodic appearance of LE cells. At the same time, there are some X-ray symptoms characteristic of rheumatoid arthritis, although very insignificant for a 12-year continuous course of polyarthritis, in the form of a small reduction in height of the wrist bones, solitary shallow wasting away of bone and tissue and osteoporosis. Overall, the favorable course of the disease attracts attention.

Patient B, age 27

She became acutely ill in September 1961, with high fever, arthralgia, pancarditis and toxicoderma upon use of antibiotics. She was treated with prednisolone, in connection with probable rheumatism, but with removal of it, her state again deteriorated; a subfebrile temperature appeared, the patient became thin, her joints ached periodically, and shortness of breath under physical stress arose. In the spring of 1963, after exposure to sunlight, the "butterfly," polyarthritis, emaciation (weight 35 kg vs. 50 kg before the illness) and falling hair appeared, and the temperature increased to 39°. A diagnosis of SLE was made, and the prednisolone treatment was renewed at 40 mg per day. Upon stopping the prednisolone, the condition worsened, and purulent meningitis developed in February 1964, which was treated with antibiotics and small doses of prednisolone.

The patient has been observed at the Institute of Rheumatism /140 since June 1964, entering with the next exacerbation: polyarthritis, lymphoadenopathy, pericarditis, lone LE cells, antibodies to DNA + at 1/30 titer, total proteins 8.7 g%, γ-globulins 34.8%. The prednisolone dose was increased to 30 mg per day. The patient was discharged upon improvement. She received a dose of prednisolone of 25 mg; however, upon reducing the dose to 10 mg, polyarthritis, polyneuritis and fever again appeared in her. Subsequently, she continually took 10-15 mg of prednisolone, increasing the dose when her condition was aggravated.

The present deterioration developed in the middle of March 1972: pains in the chest, palpitations of the heart and shortness of breath when walking, arthritis of the interphalangeal joints and pains in the feet appeared. Upon objective examination, there was vasculitis of the palms and fingertips, telangiectasia at the site of the former rash on the face, tachycardia (pulse 100 per)

min), arterial pressure 110/70 mm, slight systolic murmur at the apex.

Blood analysis: hemoglobin 12.4 g%, leukocytes 7100: ESR 28 mm, total protein 7.8 g%, γ-globulins 18.2%; LE cells were not found, antibodies to DNA at 1/10 titer ++, to nucleoproteids at 1/10 titer ++, to poly A:polyU 1:10, cryoprecipitins +; complement CH_{50} 42 units, third component β_1A 52 mg/100 ml. Antibodies to measles antigens 1/20 titer, to A_2 Hong Kong influenza virus 1/10, to influenza B virus 1/10, to parainfluenza 1, 1/10; type 2, 0, type 3, 1/40, to oncornavirus 1/40, to mycoplasma pneumonia 1/16, hominis 1/8, to adenovirus 0, to respiratory-syncytial virus 0. Upon immunoelectrophoresis, β_2-fetoprotein was revealed.

X-Ray Examination of Thoracic Cage

Sinuses do not open, diaphragm is immobile, elevated, heart displaced to the left, waist flattened, left ventricle enlarged, X-ray kymogram spikes reduced on right and left outlines.

In the patient described, with typical, but initially acute SLE, a stubborn joint syndrome is noted, in the form of recurring polyarthritis, with transient flexing contractures and obliterating polyserositis. The tendency, as in the preceding patient, to a favorable course is manifested in the absence of symptoms of erythematous nephritis, despite the almost constant high immunological activity.

Patient B, age 24

In 1959, at age 11, she suffered polyarthritis, which was interpreted as rheumatic. Soon after, during conduct of Bicillin prophylaxis, Bicillin intolerance appeared. In January 1972, a month after childbirth, temperature increased to 38-39°, arthritis of

of the left knee developed, she began to be bothered with shortness of breath and palpitations of the heart. She was treated with aspirin and Analgin, in connection with aggravation of the rheumatism, without persistent effect.

At the beginning of April 1972, after exposure to the sun, erythema, in the form of the "butterfly," a 40° temperature and sharp arthralgia appeared. SLE was diagnosed and prednisolone was prescribed at 50 mg per day. At the time of admission to the Institute of Rheumatism (26 June 1972), the prednisolone dose was reduced comparatively quickly to 30 mg.

Upon admission, there was vasculitis of the fingers, and an edematous erythema in the "butterfly" area remained, II-III polyarthritis of the interphalangeal and knee joints, systolic murmurs 5L and 4L and accent of the second tone on 2L. Pulse 72 per min, arterial pressure 110/80 mm. On the EKG, diffuse changes in the myocardium of the ventricles and in the PKG, tones of reduced amplitude. Slight systolic murmur at all points, tapered form, accent of second tone at 2L.

X-Ray Examination of Thoracic Cage

Sinuses are completely closed, diaphragm elevated, of low mobility, left ventricle enlarged. On X-ray photos of the joints, moderately expressed osteoporosis, single cyst in some ends of the metatarsal bones.

Biopsy of the knee joint synovia: chronic synovitis with nuclear pathology; nuclear corpuscles found under electron microscopy.

Blood analysis: hemoglobin 9.9 g%, leukocytes 6500; ESR 58 mm. Total protein 7.8 g%, γ-globulins 19.7%. LE cells not

detected; free-lying LE corpuscles encountered. Antibodies to DNA at 1/40 titer +, to nucleoproteids at 1/10 titer ++, latex test 1/40, Rose-Waaler reaction 1:32. Complement CH_{50} 36 units, cryoprecipitins ++. In blood serum, β_2-fetoprotein appears distinctly.

Urine without pathology.

Patient's sister has suffered discoid lupus erythematosus for 15 years.

There is no doubt of the SLE diagnosis in this patient, and it is confirmed by clinical discovery of the "butterflies" and polysyndrome condition, as well as by the high antinuclear antibody titer. It must be precisely determined whether the course of the disease is acute or chronic. Undoubtedly, the last episode is evidence of acute development of sequelae after childbirth, while the polyarthritis suffered at 11 years of age indicated in the medical history, not accompanied by formation of a heart defect, places the diagnosis of rheumatism in doubt, and, in this manner, permits this polyarthritis to be considered as the start of the basic disease. The chronic nature of the synovitis, according to morphological examination data, as well as the isolated cysts in the bones of the joints affected, are evidence in favor of the latter proposition.

Thus, all three patients are associated in development of the /141
disease at youthful ages. For two of them, one can speak of recurring polyarthritis, with a comparatively favorable course; in the first case, the matter was even of the possibility of rheumatoid arthritis or the so-called SLE borderline variant.

Further, they all associate the presence of recurring adhesive serositis (polyserositis in the first and second observations),

the absence of symptoms of active lupus nephritis with high antinuclear antibody titers, etc. One might think of the especially (in the first two patients) benign chronic version of the course of SLE. They are associated with the presence of β_2-fetoprotein in the serum.

Of what clinical value is the test for β_2-fetoprotein?

β-fetoprotein is a protein which is absent in the blood of healthy people and is a rarity in an adult person, even in pathological conditions, as was demonstrated by Uriel and colleagues. At the same time, it was developed at a high concentration in a number of SLE patients. Thus, the conjecture arises as to the possibility of use of the test for β_2-fetoprotein as an additional laboratory prognostic indicator. On the other hand, it is advisable to continue research to precisely define its diagnostic value, since β_2-fetoprotein is detected in unusual, chronic versions, in which it is not easy to make a diagnosis of SLE, as was the case with the first patient. Besides, all the patients (3) were treated for rheumatism or rheumatoid arthritis for a long time at the beginning of the disease.

There is theoretical and practical value in explaining the interrelations of β_1 and β_2 fetoproteins, as well as in comparing these components in SLE and in patients with the Luois-Bar syndrome, who also have fetal proteins in the blood.

After our first reports on β-fetoproteins, still another series of other fetal components were described in the β-band of immunoelectrophoretograms; summary data were presented by de Nechaud and colleagues.

In fact, several additional precipitation lines can be seen in the presence of very strong antisera, and this multiplicity

could even hamper reading the results. However, the remaining components, other than the two mentioned, are considerably less intense. Two components usually are developed in antiserum to neonatal β-globulins: one with β_1-band mobility ($F\beta_1$) and the other, β_2-band ($F\beta_2$). The β_1 line gives a strong reaction with benzidine, and the arc itself is flatter and less sharp, i.e., thick, but less intense (Figs. 1, 2). In benzidine stain above the cell with the sample of serum of an adult man, a benzidine-positive line and a band of considerably less intensity also are seen, making a spur to this line. The $F\beta_2$ component, which is not stained by the action of the benzidine reagent, was found in this same antiserum (see Fig. 1). Moreover, antisera obtained separately were used, one against β_1 globulins of neonatal serum and others against the β_2 fraction. As a result, some enrichment and selective strengthening of the corresponding $F\beta_1 > F\beta_2$ line, or the reverse $F\beta_2 > F\beta_1$, were observed (Figs. 3, 4). We emphasize particularly that $F\beta_2$ was always benzidine-negative. Our studies showed that the $F\beta_1$ component was not found in the serum of SLE patients.

In our preceding publication (S.S. Vasileyskiy, Yu. M. Lopukhin and R. V. Petrov, 1972), we reported the presence of β-fetoprotein in seven children suffering from ataxia-telangiectasia (Louis-Bar syndrome). We can now state precisely that this was the benzidine-positive component $F\beta_1$, which is found in more than half the patients (in six of nine patients). We did not find either $F\beta_1$ or $F\beta_2$ in the blood of healthy children of the same ages. Moreover, among these nine children with the Louis-Bar syndrome, a sharply expressed $F\beta_2$ component was found (see Figs. 3, 4). Precisely this benzidine-negative component $F\beta_2$ was found /142 in patients with SLE.

The identity of the $F\beta_2$ components in the Louis-Bar syndrome and in SLE was shown in a special test (see Fig. 2). Longitudinal $F\beta_2$ immunoelectrophoretograms with transferrin and IgA mobility

standards, are presented in Fig. 4. The migration rate coincides approximately with the mobility of IgA. The chromatogram on Sephadex G-200 showed that $F\beta_2$ emerges with fractions Nos. 7-17, while IgG peak I (Nos. 10-12) is superimposed on the middle of this band. A test for the presence of $F\beta_2$ at the beginning of this band, showing a distinct benzidine-negative $F\beta_2$ component, as well as the IgM band, not containing the $F\beta_2$ component, is presented in Fig. 1.

Beside the clinical-laboratory value of the data introduced, the immunochemical aspect attracts attention.

It is known that the normal immunoglobulin class M (β_{2-M}) consists of five subunits, each of which, in turn, has four polypeptide chains (Edelman, 1969; R. S. Nezlin, 1972). The free, monomeric IgM subunit can be produced synthetically, by chemical methods, after breaking the disulfide bonds between the subunits included in the pentameric IgM molecule, and subsequent alkylation with iodocetamide. As a result of this, the IgM_S monomer is irreversibly blocked at the C terminal by additional chemical groups ($-S-CH_2CONH_2$), and the monomer subunits cannot combined into the pentamer (Miller and Metzger; Ashman and Metzger). Beside this artifically produced and irreversibly blocked IgM_S monomer, the natural IgM_S monomer has been isolated by a number of authors. It was first found in individual cases of myeloma (Solomon and Kunkel), in ataxia-telangiectasia (Stobo and Tomasi), in a newborn child (Perchalski and colleagues) and in 17% of SLE patients (Rothfield and colleagues; Stobo and Tomasi). The conjectured IgM monomer is an intracellular precursor of the entire pentameric IgM molecule (Parkhouse and Askonas); however, it never is found outside the cells in a healthy, adult body or, consequently, in the blood serum.

Thus, the question arises: is β_2-fetoprotein not identical to IgM_S? Both proteins are normally present only in the neonatal period, both are found in SLE (in approximately 1/6 of all cases) and both appear in ataxia-telangiectasia.

However, β_2-fetoprotein, developed by antiserum to the β-fraction of neonatal serum, does not react with IgM antiserum. This possibly is due to various conditions for producing these antisera. In preparation of β-fraction antisera for neonatal sera, immunization of rabbits is carried out in the absence of the intact IgM pentamer, since this protein is present only in trace amounts in neonatal serum. Owing to this, it is possible that antibodies are developed mainly to the C_3 domain, which is open in the IgM_S monomer and closed in the intact IgM pentamer molecule. This may explain the high specificity of this antiserum.

Conclusion

The data of this study showed that β_2-fetoprotein was found in a number of SLE patients (in three of 14 examined). The preceding investigation of the authors (S.S. Vasileyskiy et al.) established a similar component in ataxia-telangiectasia, a disease with a congenital immunodeficit condition, while there was none in healthy, adult people, which permits the question to be stated as to the clinical-diagnostic value of this indicator. The advisability of clinical testing of the diagnostic value of the test flows from preliminary data on the absence of this embryonic protein in other collagen diseases. Concerning the comparative rarity (in 1/3 of the patients) of detection of β_2-fetoprotein in /143
SLE, the rarity of revealing LE cells at present should be pointed out; they are detected in many diseases, including the collagenosis group; however, this circumstance does not reduce the diagnostic value of the LE phenomenon. Further study is necessary to accumulate material on the diagnostic and, possibly, prognostic value

of developing β_2-fetoprotein, since the disease had a comparatively benign course in all three patients.

On the other hand, SLE is a natural model of an autoimmune disease system, in which immunological disorders have their "model" orderliness and, therefore, detection of the phenomenon of production of embryonic proteins in this disease is a definite additional landmark in solving a series of fundamental problems in immunogenesis.

Finally, a more direct comparison of β_2-fetoprotein with the IgM$_S$-monomer deserves attention, for future organizations of extensive clinical and theoretical studies.

REFERENCES

Ashman, P.F. and Metzger, H., J. Biol. Chem. 244, 3405 (1969).

De Nechaud, B., Economopoulos, P. and Uriel, J., Presse Méd. 77, 1945 (1969).

Miller, F. and Metzger, H., J. Biol. Chem. 240, 3325 (1965).

Nezlin, R. S., Stroyeniye i biosintez antitel [Antibody Structure and Synthesis], Moscow, 1972.

Parkhouse, P.M. and Askonos, B.A., J. Biochem. 15, 163 (1969).

Perchalski, J.E., Clem., L.W., and Small, P.A., Am. J. Med. Sci. 256, 107 (1968).

Rothfield, N.F., Frangione, B., and Franklin, E.C., J. Clin. Invest. 44, 62 (1965).

Solomon, A. and Kunkel, H., Am. J. Med., 958 (1967).

Stobo, J.D. and Tomasi, T.B., Arthr. Rheum. Dis. Abstr. 9, 543 (1960).

———, J. Clin. Invest. 46, 1329 (1967).

Tatarinov, Yu. S., Vestn. AMN SSSR (9), 68 (1970).

———, Vopr. Med. Khimii 10, 208 (1964).

Uriel, J., de Nechaud, B., Stanislawski-Birencwajg, M. et al., Presse Méd. 76, 1415 (1968).

Vasilevskiy, S.S., Byull. Eksper. Biol. (11), 48 (1965).

———, in the book Ocherki po fiziologii ploda i novorozhdennogo [Outlines in Physiology of the Fetus and the Neonate], Moscow, 1966, p. 41.

Vasilevskiy, S.S. and Yablokova, V.I., Byull. Eksper. Biol. (4), 52 (1966).

Vasilevskiy, S.S., Lopukhin, Yu.M., and Petrov, R.V., Ontogenez 3, 205 (1972).